Remarks

The Telephone Interview

The assignee, Metabolix, its representative, Dr. Joyce Hersh, and the undersigned greatly appreciate the helpful telephone interview with the Examiner on October 17, 2007, in which the amendments to the claims as shown above, were discussed.

Status of the Claims

In the Restriction requirement mailed on November 14, 2005, the claims were divided into two groups: Group I, claims 1-10, drawn to a bacterial strain, and Group II, claims 11-23,drawn to a fermentation process. In the Amendment and Response to the Restriction Requirement filed on December 14, 2005, Applicants elected the product claims, claims 1-10. However, claims 13 and 18 were amended to depend from claim 1, and so should be grouped and examined with Group 1, claims 1-8, drawn to a bacterial strain.

These claims are therefore pending and should be examined.

Rejection Under 35 U.S.C. §112, first paragraph

Claims 1-10 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Claim 1 has been amended to delete reference to a bacterial strain mutated to improve the activity of a homologous or heterologous nuclease gene without prejudice and since the subject matter is within the scope of the claims as amended. Claims 9 and 10 have been cancelled. Applicants respectfully traverse this rejection if applied to the amended claims.

The Legal Standard

The general standard for the written description requirement is that "a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." *See* M.P.E.P. § 2163(I). All that is required is that the specification provides sufficient description to **reasonably** convey to those skilled in the art that, as of the filing date sought, the inventor was in possession of the claimed invention. *Union Oil of California v. Atlantic Richfield Co.* , 208 F.3d 989, 997, 54 U.S.P.Q.2d 1227, 1232 (Fed. Cir. 2000); *Vas Cath*, 935 F.2d at 1563-64. An applicant may show possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). As noted in a recent decision by the Board of Appeals and Interferences, the written description requirement does not require a description of the complete structure of every species within a chemical genus. (*see Utter v. Hiraga*, 845 F.2d 993, 998, 6 U.S.P.Q.2d 1709, 1714 (Fed. Cir. 1988), stating "A specification may, within the meaning of 35 U.S.C. § 112, para. 1, contain a written description of a broadly claimed invention without describing all species that claim encompasses.").

An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Id.*, citing *Purdue Pharma*

L.P. v. Faulding Inc., 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000); *Pfaff v. Wells Electronics, Inc.*, 55 U.S. at 66, 119 S.Ct. at 3 11, 48 USPQ2d at 1646 (1998).

In a decision by the Board of Patent Appeals and Interferences, the Board warned that it is an improper analysis to determine that the claims are directed to an invention which is broader than that which is described in the specification since the written description is determined from the perspective of what the specification conveys to one skilled in the art citing *In re GPAC Inc.*, 57 F.3d 1573, 1579, 35 USPQ2d 1116, 1121 (Fed. Cir. 1995) and *Vas Cath*, 935 F.2d at 1563-64. Thus the Board re-emphasized that the specification need not always spell out every detail; only enough "to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation." *LizardTech Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1344-34, 76 USPQ2d 1724, 1732 (Fed. Cir. 2005).

Although the "written description" requirement is a separate requirement from the "enablement" requirement, **if the enablement requirement has been met, it is difficult for the Examiner to assert that the written description requirement has not similarly been met.** The Federal Circuit recently expressed this in *LizardTech Inc. v. Earth Resource Mapping, Inc.*, stating "A recitation of how to make and use an invention across the full breadth of the claim is ordinarily sufficient to demonstration that the inventor possesses the full scope of the invention and vice versa." *LizardTech Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1343, 76 U.S.P.Q.2d 1724, 1732 (Fed. Cir. 2005).

Analysis

The claims define a bacterial strain for production of a fermentation product selected from the group consisting of antibiotics, organic acids, amino acids, proteins, vitamins, polyhydroxyalkanoates and polysaccharides, wherein the bacterial strain is genetically modified to express a heterologous nuclease gene, wherein the nuclease gene product is secreted into the periplasmic space and released when the bacteria is lyzed by osmotic shock. Using bacterial strains, nucleases and genetic engineering techniques which are known in the art (as discussed below), the present Application describes how to produce novel organisms that secrete nuclease into the periplasmic space as claimed. The claimed organisms are beneficial in decreasing the overall fermentation process costs by increasing the recovery of the product.

Bacterial strains, such as *Ralstonia*, *Aeromonas*, *Azotobacter*, *Burkholderia*, *Comamonas*, *Methylobacterium*, *Paracoccus*, *Pseudomonas*, *Rhizobium*, and *Zooglea*, have been sold by the American Type Culture Collection in Rockville, MD and used in school laboratories and commercial fermentation facilities for many years. All are well known to be amenable to typical manipulations of bacterial genetics, allowing the use of broad host range cloning vectors as transforming vehicles for a nuclease gene of interest (see at least the paragraph bridging pages 7 and 8).

Suitable nuclease genes were well known and described in the literature with specific sources taught in the specification at least at page 6, lines 4-13, and can be obtained and produced by using well established methods in the art, such as PCR and primers complementary to the sequence encoding the nuclease using information obtained from publicly available

databases. Examples of such sequences are disclosed for many strains in GenBank (see at least page 6, lines 4-13; and page 7, lines 15-22). The Examiner has provided no reason why the disclosure of suitable nuclease genes as cited above, is not sufficient to provide a written description of the claimed genus. Once the nuclease gene has been obtained, common genetic manipulation allows for its integration into a microbial strain (see at least page 7, lines 8-10).

The present application describes how to obtain or isolate a gene encoding a nuclease of interest, modify the gene so that the encoded nuclease is secreted into the periplasmic space, and insert the gene into bacteria of interest. These strains can be screened for the desired characteristics with no further information than a simple assay for nuclease activity, or the viscosity of the resulting cell lysate. Neither requires more than routine experimentation. Example 1, describes isolation of a suitable nuclease gene (page 11, line 30 to page 12, line 20); Example 2, construction of a vector to insert the nuclease gene into a *P. putida* bacteria (page 12, line 21 to page 13, line 16), screening for nuclease expressing clones (12,000 random integrants; 1500 colonies screened; 35 nuclease expressing clones; 9 secreting nuclease); Example 3, screening of *R. eutropha* bacterial strains for secretion of nuclease (1/10 produced nuclease in the periplasm) (page 14, lines 16-23). Table 1 on page 15 shows the amount of nuclease secreted into the periplasm for six strains, of which three are high producers and one very high producer (MBX 979). Example 6, demonstrates the actual isolation of products from cell lysates from an engineered, screened bacterial strain, MBX 985, and a non-engineered strain (page 16, line 19 to page 17, line 5).

The examiner has failed to provide any evidence or reasoning as to why those skilled in the art would not extrapolate from the actual examples in the application to other strains of bacteria or other nuclease genes (see the specification at least at page 6, lines 9-10) and screen for strains expressing nuclease as Applicants have done for heterologous expression of the *Staphylococcus aureous* nucleas in *P. Putida*. Nuclease activity assays, PCR isolation of nuclease genes from chromosomal DNA, PCR isolation of nuclease genes from DNA utilizing knowledge obtained from sequences already disclosed as GenBank reference numbers, cell lysis methods to render accessible product and nuclease (if periplasmically localized), and, in general, what is already known about product recovery from bacterial strains, are all methods and relevant subject matter taught in the present specification. Applicants respectfully submit that in view of these disclosed methods and what is already known, one of skill would have no problem isolating nuclease genes and transforming a fermenting bacterial host strain.

No rationale has been presented for why the specification fails to provide sufficient written description for strains wherein the nuclease gene is integrated into a host strain selected from the group consisting of *Ralstonia eutropha, Methylobacterium organophilum, Methylobacterium extorquens, Aeromonas caviae, Azotobacter vinelandii, Alcaligenes latus, Pseudomonas oleovorans, Pseudomonas fluorescens, Pseudomonas putida, Pseudomonas aeruginosa, Pseudomonas acidophila, Pseudomonas resinovorans, Escherichia coli, and Klebsiella* (claim 7).

The specification and examples provide clear support for the entire breadth of the claimed subject matter. Therefore, all claims meet the written description requirement.

Rejection Under 35 U.S.C. § 102

Claims 1, 2, 4, 5, 6 and 8 were rejected under 35 U.S.C. § 102(b) as anticipated by Liebl, et al., *J. Bacteriology* 174(6):1854-1861 (1992) ("Liebl"). Claim 1 has been amended to recite that the nuclease gene product is secreted into the periplasmic space and released when the bacteria is lyzed by osmotic shock. Applicants respectfully traverse this rejection if applied to the amended claims

The Legal Standard

For a rejection of claims to be properly founded under 35 U.S.C. § 102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc. v Monoclonal Antibodies Inc.*, 231 USPQ 81 (Fed. Cir. 1986), cert. denied, 480 US 947 (1987); *Scripps Clinic & Research Found. v Genentech Inc.*, 18 USPQ2d 1001 (Fed. Cir. 1991). The Federal Circuit held in *Scripps*, 18 USPQ2d at 1010:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. (Emphasis added)

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. As the Federal Circuit held in *Scripps*, Id.:

> [A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove

facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference.

For a prior art reference to anticipate a claim, it must enable a person skilled in the art to make and use the invention. "A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled". *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003).

Analysis

Liebl teaches Staphylococcal nuclease (SNase) expression by various *C. glutamicum* strains, wherein the *C. glutamicum* transgenic strain is to be used for investigating protein export and processing. Liebl is concerned with investigating protein secretion in *C. glutamicum.* Liebl does not disclose the claimed bacterial strain which is genetically modified to express a heterologous nuclease gene, wherein the nuclease gene product is secreted into the periplasmic space. *C. glutamicum* is a gram positive bacterium, which does not have a periplasmic space (see for example, Sakamoto, et al., *Microbiology*, 147:2865-2871 (2001), at page 2865, right column). Thus, Liebl cannot anticipate the claimed bacterial strain. Therefore, claims 1-8 are novel over Liebl.

Rejection Under 35 U.S.C. § 103

Claims 1-10 were rejected under 35 U.S.C. § 103(a) as obvious over WO 94/10289 by Greer, et al., ("Greer"), Atkinson, et al., Biochemical Engineering and Biotechnology Handbook,

2nd Edition, Stockton Press: New York, 1991 ("Atkinson") and Lee, et al., *Adv. Biochem. Eng. Biotechnol.* 52:27-58 (1995) ("Lee"), or Miller, et al., *J. Bacteriology* 169(8):3508-3514 (1987) ("Miller") in view of Liebl or Miller. Applicants respectfully traverse this rejection.

The Legal Standard

The test for obviousness was recently reviewed and clarified by the Supreme Court in a case decided on April 30, 2007. Obviousness is a legal conclusion based on underlying facts of four general types, all of which must be considered by the examiner: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any objective indicia of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 U.S.P.Q. 459 (1966). The *Graham* analysis was recently affirmed on April 30, 2007 by the Supreme Court in *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007).

The Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a). This analysis is commonly referred to as the "TSM test". Indeed, the examiner's attention is drawn to the following quote by the Court in *KSR*:

The TSM test captures a helpful insight: A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art. Although common sense directs caution as to a patent application claiming as innovation the combination of two known devices according to their established functions, it can

be important to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements as the new invention does. Inventions usually rely upon building blocks long since uncovered, and claimed discoveries almost necessarily will be combinations of what, in some sense, is already known. There is no necessary inconsistency between the [TSM] test and the *Graham* analysis. *KSR*, 127 S. Ct. at 1727.

The obviousness analysis requires looking at the invention as a whole. "Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990); *see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986).

Hindsight analysis, such as picking and choosing from prior art references using the claimed invention as a template, has long been forbidden. *See e.g. In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988), stating "One cannot use hindsight reconstruction to pick and choose among isolated disclosures on the prior art to deprecate the claimed invention." In *KSR*, the Court also warned against the use of hindsight analysis in making an obviousness determination. The Court stated, "A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." (*KSR*, 127 S. Ct. at 1742, citing *Graham*, 383 U.S. at 36 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "'guard against slipping into the use of hindsight" (quoting M*onroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412, 141 U.S.P.Q. 549 (6th Cir. 1964)).

In response to the *KSR* decision, the Deputy Commissioner for the USPTO issued a memorandum stating: "[I]n formulating a rejection under 35 U.S.C. §103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed." Memorandum from Margaret A. Focarino to Technology Center Directors (May 3, 2007).

The case law has **clearly** established that the cited references **must** recite each and every element of the claims **as well as** provide to one of skill in the art the motivation to combine the cited references **and** provide one of ordinary skill in the art with a reasonable expectation of success. The references cited by the Examiner clearly do not satisfy these criteria.

Analysis

(a) Determination the scope and contents of the prior art

Liebl

Liebl describes the heterologous expression of a *Staphylococcus aureus* nuclease gene in the gram positive bacterium, *C. glutamicum* and the use of this transgenic system for investigating protein export in *C. glutamicum.*

Greer

Greer describes the exogenous addition of peroxide to a cell culture. As stated in the Examples of Greer, and as stated as one of the problems addressed by the presently claimed composition and methods, the exogenous addition of nucleases is generally known and too expensive to use for commodity fermentation products involving high cell density fermentations. Applicants are using elevated expression of nuclease instead of peroxide addition.

Miller

Miller teaches the use of a gram positive bacteria (*B. subtilis*) secreted nuclease for investigating "the nature of the processing of the nuclease signal peptide". Miller further characterizes the secretion of nuclease and the processing of the signal peptide from the precursor protein in *B. subtilis*.

Atkinson

Atkinson is a general review of biochemical and biotechnological methods and reagents.

Lee

Lee reports on production of PHAs in bacteria, and control of fermentation conditions.

Ascertaining the differences between the prior art and the claims

The claims require a bacterial strain that can produce both a fermentation product and secrete a nuclease into the periplasmic space, which is released when the bacteria is lyzed by osmotic shock.

Liebl does not disclose a bacterial strain genetically modified to express a nuclease gene and secrete the gene product into the periplasmic space. Liebl discloses expression in a Gram positive bacteria, which does not have a periplasmic space.

None of Greer, Miller, Lee or Atkinson or Lee makes up for this deficiency. Therefore, the prior art references, either alone or in combination, fail to teach or suggest each and every element of the claims as required under 35 U.S.C. § 103. *In re Fritch* 972 F.2d 1260, 23 USPQ2d 1780 (Fed. Cir. 1992); *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

None of Greer, Atkinson, Lee or Miller in view of Liebl or Miller provides a motivation for one of ordinary skill in the art to modify a bacterial strain as claimed. The Examiner asserted that the motivation for producing a nuclease by genetically engineered bacterial strain used in the fermentation process is provided by Greer, because Greer discloses that nucleic acids in the culture medium cause downstream processing problems, and by stating that exogenous nucleases are expensive. The Examiner's assertion is incorrect. Greer is simply stating a problem and in no way proposing a solution that requires genetic engineering. In fact, Greer proposes a precipitating agent such as polyethylene as a significantly cheaper alternative to nucleases (see Greer, page 1, lines 29-31). It is unclear how the statement that nucleases are expensive would motivate one of ordinary skill in the art to genetically modify bacteria to express high levels of nuclease, as Applicants have done, without any disclosure or suggestion as to the benefits of such a modification. Moreover, the claims require that the bacterial strain secrete nuclease into the periplasmic space, and also that the nuclease be released when the bacterial strain is lyzed by osmotic shock. Greer does not provide the motivation for one of ordinary skill in the art to make a bacterial strain which secretes nuclease into the periplasmic space, alone or in view of Liebl.

It is clear that the Examiner is using hindsight reconstruction that had been repeatedly discredited by the courts. *See i.e., In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999); *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986). The prior art does not lead one of ordinary skill in the art to have a reasonable expectation of success. The Examiner cited to Miller and Liebl as the references that provide an expectation of success, since Miller and Liebl show that it is possible to heterologously express a nuclease in different

bacterial species, specifically *C. glutamicum* and *B. Subtilis*. However, the claims as amended require that the bacterial strain be genetically modified to express a heterologous nuclease gene, wherein the nuclease gene product is secreted into the periplasmic space which *a priori* must be a ***Gram positive*** bacteria and released when the bacteria is lyzed by osmotic shock. Liebl and Miller show expression of nuclease in ***gram positive bacteria*** which do not have a periplasmic space, and so cannot provide an expectation of success with respect to heterologous expression of nuclease which is secreted into the periplasmic space and released when the bacteria is lyzed by osmotic shock. One of ordinary skill in the art cannot extrapolate from the disclosure in Miller and Liebl with respect to secretion of nuclease into the periplasmic space and then release following lysis into the culture medium with any expectation of success (see Takara, et al., J. Biol. Chem., 260(5):2670-74 (1985) a copy of which is attached). None of Lee or Atkinson makes up for this deficiency.

Accordingly, none of the claims are obvious over Greer, Aktinson, and Lee or Miller in view of Liebl or Miller.

Evaluating evidence of secondary considerations

Secondary considerations to be considered include commercial success, long felt but unresolved needs, failure of others, etc.

As stated in the specification at least at page 3, lines 21-30, nucleic acid release during fermentation processes creates significant downstream processing problems. Solutions such as exogenous nuclease addition, hydrogen peroxide or heat treatment are undesirable because, exogenous nuclease is expensive, and hydrogen peroxide or heat treatment can negatively impact

product quality. The claims provide a bacterial strain for production of a fermentation product, which is genetically modified to secrete nuclease into the periplasmic space.

Use of the claimed bacterial strains for the production of fermentation products avoids the costs associated with addition of exogenous nuclease and damage to the fermentation product from the use of hydrogen peroxide (taught by Greer) or heat is used to degrade nucleic acid released during downstream processing.

Additional Amendment to the Claims

Claim 2 has been amended to recite the limitations of claim 8. Claim 7 has been amended into an independent claim, reciting all the limitations of claim 1. Withdrawn process claim 11 has been amended to recite all the limitations of claim 1. Withdrawn claim 12 has been amended to recite the limitations of claim 21. Withdrawn claim 19 has been amended into an independent claim, to recite all of the limitations of claim 11. Claims 20 and 22-23 have been cancelled. No new matter has been added by way of these amendments

Allowance of claims 1-8, 13 and 18 as amended, and rejoinder and allowance of claims 11, 12, 14-17 and 19-21 s respectfully solicited. Claims 11, 12 and 14-17 and 19-21 are related to claims 1-8, 13 and 18 as product and process of use.

Respectfully submitted,

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